

Clinical Update

Topiramate

as a Therapy for
Chronic Posttraumatic
Stress Disorder



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ABSTRACT—Since the original publication of open-label suggestions of efficacy of adjunctive and monotherapy topiramate as a novel therapy for chronic posttraumatic stress disorder, three small, double-blind, placebo-controlled clinical trials conducted as pilot trials have been made public. The results of these studies, including efficacy, termination rates, and adverse effects resulting in termination are reviewed critically, including methodological limitations to interpretation of the findings. One study finds separation from placebo over 12 weeks for a reduction in total CAPS scores with a large effect size ($d=1.63$); a second finds significant benefit for re-experiencing but not total CAPS scores; and a third finds numerical superiority for topiramate but no significant benefit for any score reduction. Several problems, including unexpectedly high dropout rates in one study, limit the generalizability of these findings, but overall there is a signal of potential efficacy that warrants more adequately powered future clinical trials.

Topiramate,¹ an agent approved by the Food and Drug Administration (FDA) for initial treatment of partial-onset and primary generalized motor seizures and migraine headaches, has received attention for treatment of several psychiatric disorders. These disorders have included mania, bipolar depression, rapid-cycling bipolar disorder, unipolar depression, psychotic disorders, binge-eating disorder with obesity, bulimia nervosa, alcohol dependence, Tourette syndrome, and borderline personality disorder.² Despite preliminary findings of a possible antimanic effect, topiramate demonstrated no benefit compared to placebo in four large studies.³

The possibility of using anticonvulsants for anxiety disorders has stimulated considerable preliminary clinical research. Specifically, reports of anticonvulsants benefiting symptoms of posttraumatic stress disorder (PTSD) have occurred increasingly over the last two decades.

These include carbamazepine, divalproex, gabapentin, tiagabine, lamotrigine, and topiramate.⁴

Although psychotherapy has been widely used for PTSD, and the FDA has approved two serotonin reuptake inhibitors (SSRIs), sertraline and paroxetine, for treatment of PTSD, significant treatment needs remain unmet for this population. Although SSRIs outperform placebo in carefully selected populations of patients with uncomplicated PTSD, in complex cases of PTSD, such as in the combat veteran population, the extent of benefit from SSRIs alone is limited, and there are many nonresponders or partial responders.⁵ Clinical trials conducted for regulatory purposes exclude patients with psychiatric comorbidity, yet the majority of the population requiring treatment exhibits multiple comorbidities. Furthermore, some patients cannot tolerate SSRIs due to adverse effects, such as sexual dysfunction, weight gain, nervousness, sleep disturbance, fatigue, apathy, sedation, and cognitive impairment. There are also concerns

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about the limited benefit of SSRIs even in initial responders due to the “poop out” effect seen with those agents; cessation of effectiveness over time may not provide adequate long-term control of the symptoms of a chronically relapsing disorder, such as PTSD. Finally, although not well studied, the population of patients with comorbid bipolar disorder and PTSD poses a special challenge: Although some such patients may tolerate antidepressants, concern about the risk of mood destabilization raises a red flag about using this class of medication. These larger clinical concerns have stimulated interest in finding nonantidepressant agents as alternatives for the treatment of PTSD. Topiramate has been one such agent.

EARLY CLINICAL EXPERIENCE

Early case series. In 1996, based on serendipitous observations, the author began to use topiramate for treatment-resistant chronic PTSD in civilian patients in private practice and in a public sector mental health clinic. When patients persisted in reporting symptom control, a retrospective chart review⁶ described a pattern of predominantly positive responses for reexperiencing symptoms, and the author began to explore topiramate's effects on avoidance and hyperarousal symptoms.

This naturalistic study in 35 patients with nonhallucinatory PTSD ($n=28$) and hallucinatory PTSD ($n=7$) included eight nonhallucinatory patients with bipolar disorder. The study lasted a mean duration of 33 weeks, with a range of 1 to 119 weeks. Overall, topiramate suppressed nightmares in 79 percent of the patients and intrusive memories and flashbacks in 86 percent.

Patients with hallucinatory PTSD had a somewhat lower response rate, particularly for persistent suppression of reexperiencing symptoms. Median time to full suppression of nightmares and hallucinations was eight days. The last 17 nonhallucinatory patients also received pre- and post-treatment Posttraumatic Stress Disorder Checklists (PCL-C). The PCL-C is a self-report scale that reportedly shares similar reliability with the Clinician-Administered PTSD Scale (CAPS) ($\kappa=0.9$). Total PCL-C scores reduced from 60 at baseline to 39 at Week 4, which translates to a 49-percent reduction in PTSD symptoms (as calculated on the basis of no symptoms on the PCL-C equalling 17). The PCL-C data suggested a positive effect for avoidance and hyperarousal symptoms as well as for reexperiencing symptoms. The PCL-C data suggested a positive effect for avoidance and hyperarousal symptoms as well as for reexperiencing symptoms. Response rates were similar for add-on treatment ($n=28$) and monotherapy ($n=7$). There was a 63-percent completion rate, with 26-percent discontinuing due to adverse events of eating cessation, acute narrow-angle glaucoma, headache, overstimulation/panic, emergent suicidal ideation, and memory concerns.

Prospective open clinical trial. On the basis of the findings of the naturalistic retrospective chart review, a prospective open-label trial was conducted in a totally new sample of patients, using the PCL-C as the primary outcome measure.⁷

This study was entirely done in a private setting, using 33 outpatients with DSM-IV diagnosed chronic PTSD. It excluded individuals with

hallucinatory symptoms to avoid confusion with psychotic disorders. Thirty patients completed both baseline and Week 4 PCL-C reports. Add-on occurred in 28 patients, and five received monotherapy. Overall, there was a 49-percent reduction in PTSD symptoms (62.6 at baseline and 40.3 at Week 4). Age, sex, bipolar comorbidity, age at onset of PTSD, duration of PTSD symptoms, severity of baseline PCL-C score, and monotherapy versus add-on medication status did not predict reduction in PTSD symptoms. Median time to full response for reexperiencing symptoms was nine days, and median dosage was 50mg/day at the onset of full suppression of reexperiencing symptoms. Twelve patients (36%) discontinued medication, with seven (21%) discontinuing due to adverse events of overstimulation, clumsiness, cognitive impairment, and headache, and five (15%) discontinuing for other reasons, including lack of relapse of PTSD following interruption of medication in four patients (12%).

The similarity of PTSD symptom reduction rates in both the retrospective and prospective studies (-49%) supported the hypothesis that topiramate might be helpful for chronic PTSD in civilians. The absence of a placebo-controlled group or active comparator, however, made interpretation of the significance of these observations difficult.

Controlled clinical trials.

Since publication of the open-label studies, three double-blind, placebo-controlled clinical trials for the acute treatment of chronic PTSD have been made public. The following review will simply review the findings from the three available studies. Due to the small number of studies and variability in methods, the studies are not

TABLE 1. Key findings of the controlled trials on topiramate

Author (year)	<i>n</i>	Reductions in Total CAPS Scores (topiramate v. placebo)	<i>p</i>	Effect Size	Withdrawal Rates from Topiramate	Comments
Akuchekian (2004)	67	37.4% v. 4.7%	<0.00	1.63	2/34 (5.9%)	Add-on for treatment-resistant patients.
Tucker (2005)	38	59.5% v. 45.5%	<0.217 (NS)	-	5/19 (26.3%)	Monotherapy. Excluded major depression, major anxiety disorders. Separated on reexperiencing cluster.
Petty (2005)	68	39.5% v. 29.5%	NS	-	20/34 (58.8%)	Monotherapy. Included major depression, major anxiety disorders.

deemed suitable for meta-analysis at this time.

The first controlled trial consisted of a randomized trial of topiramate versus placebo in 67 combat veterans performed at the Isfahan University of Medical Sciences⁸ in Iran. These subjects had a mean duration of illness of 17.9 years. The locus of treatment was not mentioned. This study suggested a robust overall effect of topiramate, principally accounted for by improvement in reexperiencing and arousal symptoms. These patients had been judged nonresponsive to other psychotropic drugs for at least six months. This was an add-on study for a 12-week period. Primary outcome measure was the 11-item [sic] severity score of the CAPS. Topiramate, compared to placebo, significantly reduced both the intensity and frequency of reexperiencing symptoms (intrusive memories, nightmares, flashbacks), insomnia, irritability, anger, the frequency of difficulty with recall, and the intensity of startling. Percentage reductions in total CAPS scores were 37.4 percent for topiramate

(50.7 to 32.75) and 4.7 percent for placebo (48.9 to 46.62) (independent t-test, $p < 0.00$). The calculated effect size for this difference is 1.63, a large effect.⁹ Analysis of the clusters for PTSD revealed significant improvement compared to placebo for both reexperiencing and arousal clusters but not avoidance. There were few dropouts: Two out of 34 randomized to topiramate dropped out due to side effects of sexual dysfunction, lightheadedness, and dizziness. The authors opined that some side effects might have come from the concomitant psychotropic medications patients were taking.

Investigators at the Oklahoma Health Sciences Center, University of Oklahoma,¹⁰ report a 12-week, double-blind, randomized, placebo-controlled trial of monotherapy topiramate in 38 outpatients with civilian, noncombat PTSD. Mean duration of illness was not specified, but inclusion criteria required persistent PTSD greater than six months duration. Median final dose of topiramate was

150mg/day; mean treatment duration was 76 days. The primary outcome measure was the 17-item severity score of the CAPS, assessed for intent-to-treat. Topiramate demonstrated a numerically superior response than placebo on the primary outcome measure (-59.5% compared to -45.5%) but did not achieve significance ($p < 0.217$). On secondary measure analysis, however, there were statistically significant reductions in reexperiencing cluster symptoms of the CAPS (-74.9% compared to -50.2% for placebo, $p = 0.038$), in TOP-8 overall severity scores (-68.0% compared to 41.6 percent for placebo, $p = 0.025$), and near significance in CGI-I mean scores ($p = 0.055$). By the end of the trial, five (26%) withdrew from the study (compared to 16% for placebo), four of them due to side effects of emotional lability, nervousness, rectal bleeding, and aggravated depression.

A multisite study at Creighton University in Nebraska and Fieve Clinical Services in New York¹¹ presented a similar study design to the University of Oklahoma

study: a 12-week, placebo-controlled, randomized clinical trial of monotherapy topiramate in 72 outpatients with noncombat PTSD. Sixty-eight men and women entered the ITT population. Duration of illness was not specified. Median final daily topiramate dose was 100mg/day, and mean treatment duration was 55.3 days. The primary outcome measure was change in the 17-item total severity score of the CAPS from baseline to the last visit of the double-blind phase. Topiramate

termination was loss to follow-up (topiramate 29%, placebo 3%); six (18%) discontinued because of adverse effects, compared to nine (26%) on placebo. Adverse effects attributed to topiramate discontinuation that occurred more often than with placebo included paresthesias, fatigue, diarrhea, flu-like symptoms, nausea, anorexia, cognitive problems, and thirst. This study is very difficult to interpret due to the high number of patients lost to follow-up in the topiramate group.

avoidance or arousal symptoms.

Interpretation of the negative findings needs to be tempered with caution. The very low completion rate of the Creighton University study (41% for topiramate) makes interpretation of intent-to-treat findings susceptible to error. Before rejecting the hypothesis, it might be useful to reanalyze that data set with the mixed models repeated measures (MMRM) method, which some statisticians believe is superior to the last-observation-carried-forward

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reduced the primary outcome measure 39.5 percent compared to 29.5 percent for placebo, not significant. On secondary measure analysis, there were numerically superior results for topiramate for all PTSD clusters (reexperiencing, -43.6% vs. -34.8%; avoidance, -38.3 vs. -30.6; hyperarousal, -36.6% vs. -21.4%) but none achieved statistical significance. Other secondary measures, including CGI, demonstrated no significant difference compared to placebo. By the end of the trial, only 41 percent of the topiramate group remained in the study, compared to 51 percent on placebo. The chief reason for early

DISCUSSION

The original hypothesis about topiramate's benefit for PTSD remains under examination, with some evidence supporting it and other evidence failing to add support.

The strongest evidence to date includes the positive double-blind controlled trial in combat veterans from Iran, which suggests that topiramate may be an effective add-on agent in medication-refractory patients with chronic PTSD. There is also evidence from one well-executed trial that monotherapy topiramate may be helpful for reexperiencing symptoms of PTSD but not necessarily for

method when there are numerous missing values due to premature termination.¹² Even this method may prove inadequate to surmount the problem of a 29-percent rate of subjects lost to follow-up with topiramate.

Furthermore, the Oklahoma study highlights the problem that a high placebo-response rate poses in interpreting findings. It is quite remarkable that placebo reduction of scores on the CAPS can vary from as small as -5 percent in the Iranian study to -46 percent in the Oklahoma study.

The presence of comorbid depression may also confound study outcomes. Some symptoms

of PTSD—especially avoidance and hyperarousal symptoms in contrast to reexperiencing symptoms—potentially overlap with similar symptoms seen in major depression, including social withdrawal, numbing of pleasure, impaired concentration, insomnia, and irritability. Assessment of the proper classification of these symptoms as due to PTSD rather than depression requires the interviewer to make judgments of causality, which can be very difficult, especially if there is both major depression and PTSD coexisting independently. The Oklahoma study excluded patients with primary major depressive and major anxiety disorders; the Creighton study did not exclude such patients. Perhaps the Iranian study's better response rates were due to the use of concomitant medications to reduce comorbid psychiatric symptoms.

There are other differences between the Iranian study and the two American studies that need further consideration. The Iranian study was an add-on study, whereas the American studies were both monotherapy. Furthermore, the Iranian study was confined to medication-resistant patients, whereas the American studies did not specify treatment resistance for inclusion. Finally, the Iranian study included patients with longstanding persistent illness (similar to the open-label studies), but it is unclear if the American studies included patients with a shorter duration of illness.

Finally, in assessing the issue of methodological limitations to these studies, the matter of underpowered studies must be addressed. In the three double-blind trials, the number of patients randomized to topiramate was 34, 19, and 34; the number of patients

completing the studies on topiramate was 32, 14, and 14. These are surely small numbers, making any separation from placebo difficult to demonstrate and the possibility of a Type II statistical error a substantial possibility.

CONCLUSION

In conclusion, the hypothesis that topiramate may be an effective agent for PTSD remains alive. The negative findings that exist are troubled by methodological problems, including inadequately powered studies, high discontinuation rates, confounding with comorbid depression, and high placebo response rates. The presence of one positive controlled trial, one negative (or, more likely, missed) trial showing numerical superiority for reduction of total CAPS scores and statistical significance for reduction of reexperiencing symptoms, and all three showing numerical superiority of topiramate for total CAPS score reductions and reductions in all three PTSD subscales (reexperiencing, avoidance, and arousal) when taken together argues for further, more adequately designed and executed clinical trials.

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inhibits glutamatergic activity via negative modulation of α -amino-2-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and kainite receptors. It also has agonist effects on novel GABA receptors. Direct and indirect effects on gabenergic and glutamatergic transmission theoretically may affect fear responses through inhibiting exaggerated responses from an overexcited amygdala and associated fear circuitry.

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